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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,992	09/27/2006	Torsten Dunkern	27577U	4187

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,992	DUNKERN ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 11/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on November 14, 2008.

Status of Claims

Claims 21-28 are currently pending and are the subject of this office action.

Claims 21-28 are presently under examination.

The following species elected on the reply filed on January 7, 2008 are under examination: Sepsis Associated Encephalopathy (SAE) as the disease associated with or based on impairment or dysfunction of cerebral vascular reactivity. Since the elected species for PDE5 inhibitor: Sidenafil is free of prior art, the search was expanded to the remaining PDEV inhibitors, which are also free of prior art.

Priority

The present application is a 371 of PCT/EP05/250958 filed on 03/03/2005, and claims priority to EPO 04100909.3 filed on 03/05/2004.

Claim Rejections - 35 USC § 112 (New Rejection not Necessitated by Amendment)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating SAE with Sidenafil, does not reasonably

provide enablement for treating SAE with any other PDEV inhibitor, nor does provide enablement for prophylaxis of SAE with Sidenafil or any other PDEV inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 21-28 recite a method for the treatment or prophylaxis SAE (species elected) with a therapeutically effective amount of a PDEV inhibitor.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

For this discussion, the word prophylaxis is considered a synonym of the word prevention.

As illustrative of the state of the art regarding the treatment and/or prophylaxis of SAE with PDEV inhibitors, the examiner cites: applicant's own admissions, Wratten (European Journal of Anaesthesiology (2008) 25 (Suppl. 42): 1-7, cited in prior office action), Wilson (Neurol. J. Southeast Asia (2003) 8:65-76) and Bischoff (International Journal of Impotence Research (2004) 16:S1-S14).

Pathophysiology of SAE is not understood, and might be multifactorial. Indeed, brain dysfunction is sepsis may be related to action of micro-organisms toxins, to the effects of inflammatory mediators, to metabolic alterations and to abnormalities in cerebral circulation. At this moment a specific treatment for SAE does not exist and outcome relies upon prompt and appropriate treatment of sepsis as a whole (Green et. al., Front. Biosci. (2004) 9:1637-1641, mentioned by applicant, see specification end of page 8 and beginning of page 9).

Wratten teaches approaches to reduce systemic inflammation in septic-associated neurologic complications. He teaches that although the aetiology of septic encephalopathy has not been clearly established, systemic inflammation appears to play a key role in altering both the blood-brain barrier permeability and amplifying the inflammatory response. Several new therapies are now aimed at reducing systemic inflammation like coupled plasma filtration adsorption which consists of the non-specific removal of cytokines and mediators involved in systemic inflammation and immune suppression by the use of plasma filtration coupled to an adsorbent resin cartridge with high affinity for many cytokines and mediators (see abstract).

Wilson teaches that the mechanism of SAE is uncertain. In advanced cases it is likely multifactorial, given the variety of pathological findings. The early, fully reversible cases are not likely associated with structural change and are probably metabolic in nature. Other mechanisms, in addition to the metabolic disturbances, operate in more advanced cases (see page 65, right column, last paragraph). Wilson, then lists a series of proposed mechanisms that have been proposed, like: microvascular disorder, amino acids and neurotransmitter imbalance, etc (see pages 66 through 68). Among the current therapies the author mentions: antibiotics, however most of the antibiotics fail for several reasons (see page 70, right column, fourth paragraph); drugs or agents like activated protein C (see page 70, right column, fifth paragraph) and then future therapies like combining antibiotics with drugs that slow the production of reactive Nitrogen and Oxygen species triggered by septic insults (see page 70, right column, sixth paragraph).

In summary, there is still no successful method for the prevention or treatment of SAE and there is definitively no teaching in the prior art as to whether PDEV inhibitors could be potentially useful for the treatment or prevention of SAE.

Regarding the potency and selectivity of the best well known PDEV inhibitors, Bischoff teaches that although tadalafil, sildenafil and vardenafil all act by inhibiting the PDE5 enzyme, these drugs also inhibit other PDE enzymes. For example: Sildenafil and vardenafil inhibit PDEVI, an enzyme found in the eye, more than tadalafil. Sildenafil and vardenafil also inhibit PDE1 more than tadalafil. PDE1 is found in the brain, heart, and vascular smooth muscle. It is thought that the inhibition of PDE1 by sildenafil and

vardenafil leads to vasodilation, flushing, and tachycardia. Tadalafil inhibits PDE11 more than sildenafil or vardenafil. PDE11 is expressed in skeletal muscle, the prostate, the liver, the kidney, the pituitary gland, and the testes. The effect on the body of inhibiting PDE11 is not known (see entire document).

4. The breadth of the claims

Some claims, like claims 21-23 and 26 are very broad in terms of the PDEV inhibitors claimed, while others like claims 24-25 and 27-28 claim only: sildenafil, vardenafil and/or tadalfil. Applicant is reminded that SAE is the only species being examined regarding diseases associated with or based on impairment or dysfunction of cerebral vascular reactivity

5. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides animal data for the treatment of SAE with Sildenafil in rats (see example 3 on page 12) proving the efficacy of Sildenafil in this particular animal model. The specification provides no data for any other PDEV inhibitor, nor provides any data for the prevention of SAE.

6. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled

artisan would not accept that the instantly claimed genus of compounds encompassed by all PDEV inhibitors will prevent (including Sildenafil) or treat (except for Sildenafil) SAE.

Since there is no precedent in the literature for the treatment or prevention of SAE with any PDEV inhibitor, and since Applicant only provided data for Sildenafil in an animal model known to correlate with the treatment of SAE, but no data for any other PDEV inhibitor, and since the prior art teaches that sildenafil partially inhibits other PDE enzymes and has a different specificity profile than the other two best known PDEV inhibitors: vardenafil and/or tadalfil, the skilled physician will have to engage in undue experimentation when treating SAE with any other PDEV inhibitor (except for sildenafil), since applicant was not be able to show a direct correlation between PDEV activity *in vitro* and efficacy against SAE *in vivo*. This would require formulation into a dosage form, and testing in an assay known to correlate to the efficacy of such treatment. This is considered undue experimentation.

7. Conclusion

Accordingly, the inventions of claims 21-28 do not comply with the scope of enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 112, first paragraph (enablement).

Applicant's arguments have been fully considered and they are persuasive.

Rejection under 35 USC 112, first paragraph (enablement) is withdrawn. However, a new rejection under 35 USC 112, first paragraph (scope of enablement) not necessitated by amendment (see above) was applied.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
February 16, 2009

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642